REMARKS/ARGUMENTS

Claims 1 to 6 are pending in this application. Applicants are herein canceling claims 7-19 in order to comply with the election of the Group I invention. Applicants reserve the right to prosecute the claims of non-elected groups in future continuing or divisional applications.

Formal matters

As of this date, Applicants have not received an initialed IDS from the Examiner. Applicants therefore respectfully request an initialed Form 1449.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse because there is no evidence of record so much as suggesting that those skilled in the art would be unable to practice the claimed invention.

The enablement requirement of 35 U.S.C. § 112 mandates that the specification teach those skilled in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The test of enablement is **not** simply whether experimentation would have been necessary, but whether such experimentation would have been **undue**. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. Any conclusion of non-enablement must be based on the evidence as a whole. *Id.*

The Examiner bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide reasonable expectation as to why scope of protection provided by claim is not adequately enabled by disclosure); MPEP §2164.04. A specification **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *Id.* at 224. As stated in the MPEP:

> [I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 370.

The present rejection does not satisfy this standard. In particular, the Action presents no art-supported substantiation of its assertions. Rather, it sets forth only a general assertion that the art of biotechnology is a highly unpredictable art and that it would be an undue burden for a skilled practitioner to test any and all pH buffering agents and tonicity agents to see if they work in the claimed invention. Applicants respectfully disagree. Buffering and tonicity agents are well known, as are general methods of using them and combining them with various therapeutic agents, including proteins, for administration. The Action provides no reason to believe that a skilled practitioner would have any difficulty in choosing an appropriate pH buffering and/or tonicity agent for use in the present invention. There is a vast amount of literature describing such agents and methods of using them in pharmaceutical compositions.

The present invention relates, in part, to the discovery that the sustained-release of erythropoietin can be achieved by administering to a subject a pharmaceutical composition comprising erythropoietin, sodium carboxymethyl ether cellulose, a pH buffering agent, and a tonicity agent. The present inventors are believed to be the first to realize the benefits that can be obtained by pharmaceutical compositions comprising both erythropoietin and sodium carboxymethyl ether cellulose. Applicants respectfully submit that the optimization of such compositions by the addition of pH buffering agents and tonicity agents can be performed by any skilled practitioner armed with the knowledge of the art and the present specification.

The Action's assertion of undue breadth appears to be based on an assumption that enablement requires an exemplification of all possible variations of the claimed invention, *e.g.*, in this case, the showing of pharmaceutical compositions comprising all known tonicity agents and buffering agents. Such a requirement, however, is not consistent with the patent laws. Using the conditions set forth in the claims, the teachings of the specification, and routine methodology, any competent technician would be able to prepare the claimed pharmaceutical compositions. According to MPEP § 2164.02, "Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." Enablement requires only that the application teach how to make and use the invention without undue experimentation. *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977).

Because the Action fails to identify any reason why a skilled practitioner, following the methods described in the present application, would be unable to prepare the claimed pharmaceutical compositions, Applicants submit that claims 1-6 are sufficiently enabled.

Accordingly, Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ritchey *et al., Blood*, 1981, 57(4), 788-793 (Ritchey reference). The Action, however, has yet to show that the Ritchey reference anticipates the claimed invention.

For a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

The Action cites the Ritchey reference as the basis for the 102(b) rejection yet fails to identify in the reference each and every element of the claimed invention, *e.g.*, a pharmaceutical composition comprising erythropoietin **and** sodium carboxymethyl ether cellulose. In the Ritchey reference, 2 IU of human urinary erythropoietin was added to a cell culture containing bone marrow cells and peripheral cells. There is no indication that the erythropoietin was in a pharmaceutical formulation or that it was added to the cell culture in

combination with any additional agents (see p788, column 2). Moreover, the only mention of carboxymethyl cellulose made in the reference is to the purification of globin chains using carboxymethyl cellulose column chromatography. Accordingly, as the Action fails to identify anything in the cited references that teaches each and every element of the present invention, *i.e.,* a pharmaceutical composition comprising erythropoietin, sodium carboxymethyl ether cellulose, a pH buffering agent, and a tonicity agent, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

First rejection under 35 U.S.C. § 103

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sytkowski (U.S. Patent No. 5,747,446), Chiba *et al.* (U.S. Patent No. 3,865,801), Chiba *et al.* (U.S. Patent No. 4,465,624), Woog *et al.* (U.S. Patent No. 5,503,827), Sytkowski *et al.* (U.S. Patent No. 5,919,758), or Sytkowski *et al.* (U.S. Patent No. 6,107,272) taken with Casas (U.S. Patent No. 4,548,952), Yamada *et al.* (U.S. Patent No. 4,705,805), or Ishikawa *et al.* (U.S. Patent No. 4,596,806). Applicants submit that a proper *prima facie* case of obviousness under 35 U.S.C. § 103(a) cannot be set forth over the cited references for the reasons set forth below.

The Action characterizes the Sytkowski, Chiba, and Woog patents as teaching pharmaceutical compositions containing erythropoietin, sodium phosphate, and sodium chloride and the Casas, Yamada, and Ishikawa patents as teaching the use of CMC in pharmaceutical compositions. According to the Action, it would have been obvious to one of ordinary skill in the art to prepare a pharmaceutical composition containing all four ingredients. In response, Applicants respectfully traverse.

A. A Proper Prima Facie Case of Obviousness Has Not Been Set Forth

To construct a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See*, MPEP § 2142. Moreover, to avoid the pitfall of hindsight, the Examiner must "identify ***specifically*** . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them," *In re Rouffet* 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). Applicants respectfully submit that each of the required criteria set forth above has not been satisfied, thus, a *prima facie* case of obviousness has not been set forth.

As discussed above, the present invention is based, in part, on the discovery that the sustained-release of erythropoietin can be achieved by administering to a subject a pharmaceutical composition comprising erythropoietin, sodium carboxymethyl ether cellulose, a pH buffering agent, and a tonicity agent. Accordingly, the present claims are directed to pharmaceutical compositions comprising erythropoietin, a pH buffering agent, a tonicity agent, and sodium carboxymethyl ether cellulose. In direct contrast, the Casas, Yamada, and Ishikawa references are directed to pharmaceutical compositions comprising phenylacetoxyacetyl derivatives, benzamide derivatives, or piperidino-tetrahydroimidazo-quinazolin-one derivatives, **not to proteins or polypeptides.** There is no specific suggestion that CMC and erythropoietin should be combined *per se* and/or that the combination would give rise to a reasonable expectation of success. It appears to be the Action's position, that

because CMC has been used as an ingredient in a pharmaceutical composition, it would be obvious to use it as an ingredient in any pharmaceutical composition. Applicants contend that such a position is untenable. Erythropoietin possesses different functionalities and characteristics from the phenylacetoxyacetyl, benzamide, and piperidino-tetrahydroimidazo-quinazolin-one derivatives disclosed in the cited patents and thus cannot be expected to act in the same manner. Moreover, there is no indication in the cited references that CMC acts as a sustained release enhancing agent or that it would be desirable to add it to a pharmaceutical composition comprising a protein such as erythropoietin.

As noted in the action, the Sytkowski, Chiba, and Woog patents do not teach pharmaceutical compositions comprising both erythropoietin and CMC. Nor do the references suggest the need for a sustained release enhancing agent in their disclosed formulations.

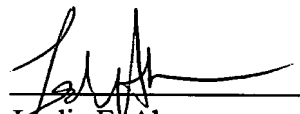
Applicants submit that there is simply no motivation provided in the cited references to prepare a pharmaceutical composition comprising CMC, erythropoietin, a pH buffering agent and a tonicity agent. In addition to a lack of sufficient motivation to combine both erythropoietin and CMC in a pharmaceutical composition, there is also no reasonable expectation of success that such a composition would possess pharmacokinetic properties suitable or desirable for administration to a subject. Accordingly, Applicants respectfully submit that, in addition to the lack of motivation to combine the cited references, the cited references fail to provide a reasonable expectation of success. As such, Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. § 103(a) as allegedly unpatentable over the Sytkowski patents, the Chiba patents, and the Woog patent taken with the Casas, Yamada or Ishikawa patents be withdrawn.

Second rejection under 35 U.S.C. § 103(a)

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ritchey taken with the Sytkowski, Chiba, and Woog patents. Applicants respectfully traverse. As set forth above, the Ritchey reference neither teaches nor suggests the use of both CMC and erythropoietin in a pharmaceutical composition. As noted in the action, the Sytkowski, Chiba, and Woog patents also do not teach the use of both CMC and erythropoietin in a pharmaceutical composition. Accordingly, Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. § 103(a) as allegedly unpatentable over the Ritchey reference taken with the Sytkowski, Chiba and Woog patents be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Date: September 22, 2003



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